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Leena Ullén

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NEW IMPROVED FORMULATION

TECHNICAL FIELD

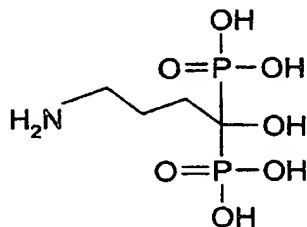
5 The present invention relates to pharmaceutical formulations comprising bisphosphonates. The invention also relates to a process for preparing such pharmaceutical formulations, to the use of such pharmaceutical formulations for inhibition of bone resorption and for the treatment and prevention of osteoporosis.

10

BACKGROUND ART

Bisphosphonates

15 Bisphosphonates are carbon-substituted pyrophosphate analogues that include potent inhibitors of bone resorption, such as alendronate (4-amino-1-hydroxybutylidene-1,1-biphosphonic acid) (Sato et al. (1991) J. Clin. Invest. 88, 2095-2105).



alendronate

20

The oral bioavailability of bisphosphonates (etidronate; clodronate; pamidronate; alendronate) in humans lies between 1% and 10% according to Lin (Bone 18, 75-85, 1996) and absorption is diminished when given with meals, especially in the presence of calcium. Therefore bisphosphonates should never be given at mealtime and never together
25 with milk or dairy products according to Fleisch (Bisphosphonates in bone disease, Stampi

& Co., Bern 1993, p.50, and references cited therein). In Dowty M.E. et al, Pharm. Sci. Suppl., Vol 1, No 1: 448 (1998) the low permeability of risedronate is disclosed.

The oral bioavailability of alendronate has been studied by Gertz et al. (Clinical Pharmacology & Therapeutics, vol. 58, pp. 288-298, 1995). It was found that taking alendronate either 60 or 30 minutes before breakfast reduced bioavailability by 40% relative to a 2-hour wait before a meal. Taking alendronate either concurrently with or 2 hours after breakfast drastically (>85%) impaired availability. A practical dosing recommendation, derived from these findings was that patients should take the drug with water after an overnight fast and at least 30 min before any other food or beverage.

Moreover, the labeling information on an existing commercial formulation of alendronate (FOSAMAX[®]) contains a warning that the formulation, like other bisphosphonates, may cause local irritation of the upper gastrointestinal mucosa. This clearly shows that a solution to the problems associated with the poor and variable absorption of orally administered bisphosphonates known for a long time has not yet been found.

Consequently, there is a need for pharmaceutical formulations comprising bisphosphonates, such as alendronate, which reduces the above mentioned drawbacks and allows the patient to take the medicament more conveniently, e.g. together with food intake.

Absorption enhancers

Pharmaceutical excipients may be classified as functional or not-functional (M E Aulton: Pharmaceutics - The science of dosage form design, Churchill Livingstone 1988, Hong Kong). Not-functional excipients are, e g, binders, fillers, dryers etc and are used to fulfill pharmaceutical technology aspects of the formulation as size, hardness, appearance (e g colour) etc. Functional excipients on the other hand are utilized, e g to achieve certain types of release profiles such as immediate release, extended release, controlled release etc by the

use of rapidly or slowly hydrating, swelling, eroding, etc polymer materials; to achieve fast dissolution of the drug by incorporating surface active substances; to achieve control of the pH in the formulation or in the immediate environment of the drug by the usage of buffers in the formulation; etc.

5

Another important aspect of excipients is the influence from functional excipients on the biological environment that can be obtained with certain substances, often called enhancers in the literature, by for example changing the permeability of the biological membrane, to inhibit complex formation with biological substances present (e g proteins, lipids, bile salt, ions), etc. The rational for the use of such excipients is then to achieve, e g higher
10 availability, less variation in absorption due to, e g food interactions (Charman WN et al. J Pharm Res 86 (3): 269-282 (1997)) avoidance of instability in GI-environment, to diminish drug influence on membrane integrity etc. Comprehensive reviews on the effect of enhancer agents and their use in pharmaceutical formulations have been presented by E J
15 van Hoogdalem et al (Pharm Theor vol 44, 407-443 (1989)); by S Muranishi et al (Crit Rev Ther Drug Carrier Syst vol 7, 1-33 (1990)); by E S Swenson and W J Curatolo (Adv Drug Deliv Rev vol 8, 39-92 (1998)); in drug Absorption Enhancement (Ed: A B G de Boer, Harwood Academic Publishers 1994); in Baughman RA et al Circulation 98 (16): 1610-1615 (1998); in Bai JP et al, Crit Rev Therap Drug Carrier Syst 12(4): 339-371 (1995); in
20 Bowe CL et al, Proc Nat Acad Sci 94 (22): 12218-23 (1997); in Chao AC et al, J Pharm Sci 87(11): 1395-1399 (1998); in Chao AC et al, J Drug Targeting 6(1): 37-43 (1998); and in Fix JA. J Pharm Sci 85(12) 1282-1285 (1996).

25

In many circumstances the enhancers combine several different effects. However, the degree of influence on the biological environment is seldom known á priori, and mechanisms behind the effects are obscure and difficult to ascertain in-vivo. The different types of such functional excipients includes e g lipids, chelators, and polymers which all may act, e g by preventing or enhancing complexation with species from the biological environment (e g proteins, bile salts, lipids, ions like Ca^{2+} etc), by influencing the
30 membrane permeability in a reversible or irreversible manner, by presenting the drug in

small particulate form and thereby avoiding high local concentrations that might be irritating near the membranes of the drug, etc.

5 DISCLOSURE OF THE INVENTION

It has surprisingly been found that the absorption of bisphosphonates can be substantially improved by incorporating one or more additives in pharmaceutical formulations containing bisphosphonates. The use of additives as enhancers will result in positive
10 synergistic effects, such as enhanced and/or less variable absorption when bisphosphonates, e.g. alendronate, is given by different administration routes, such as the oral, the rectal, the buccal, the nasal and the pulmonary route. It will allow the patient to take the medicament more conveniently, e.g. together with food intake. It will also reduce side-effects as local irritation of, e.g. the upper gastrointestinal mucosa.

15

Therefore, an object of the present invention is to provide a pharmaceutical formulation comprising at least one bisphosphonate and one or more additives selected from the group consisting of

- a surfactant, such as a nonionic surfactant, e.g., a sorbitan ester (Span series), a
20 polysorbate (Tween series), a poloxyethylated glycol monoether (like the Brij series), a polyoxylated alkyl ester (Myrj series), a polyoxyethylated alkyl phenol (like the Triton series), an alkyl glucoside, like sugar glycosides, e.g., dodecylmaltoside, sugar fatty acid esters, e.g. sucrose laurate, sucrose monostearate and saponins;
- an ampholytic surfactant, e.g., a betaine;
- 25 - an anionic surfactant, e.g., a sulphated fatty alcohol, a sulphated polyoxyethylated - alcohol, others like dioctyl sulphosuccinate;
- a cationic surfactant, e.g., an ammonium compound;
- a bile salt, such as a dihydroxy bile salt like sodium deoxycholate, a trihydroxy bile salt like sodium glycocholate and fusidates, e.g., sodium dihydrofusidate;
- 30 - a soap and a fatty acid, and a salt thereof, e.g. octanoic acid, decanoic acid and sodium decanoate;

- a lipid (with the exception of those disclosed in PCT application no. SE98/01790), such as a phospholipid, e.g., DPPC and DMPC;
- an oil, e.g., soy bean oil and sunflower oil;
- an enamine, such as DL-phenylalanine and ethylacetoacetate enamine;
- 5 - a chelating agent, e.g., EDTA, EGTA, and citric acid;
- a phenothiazine, such as chlorpromazine;
- a fatty acid derivative of carnitine and peptides, e.g., palmitoyl-DL-carnitine;
- a substance selected from the group consisting of azone, concanavalin A, a phosphate and a phosphonate derivative, such as DL - α -glycerophosphate and 3-amino-1-
- 10 hydroxypropylidene-1,1-diphosphonate, diethyl maleate and diethylethoxymethylene malonate;
- a product from Maillard reactions, e.g., a compound from a glucoselysine reaction;
- a polymer, such as a polyacrylic acid, e.g., Carbopol[®], polycarbophil;
- a chitosan and a chitosan derivative; and
- 15 - a block copolymer, e.g., a poloxamer, poloxamine, and meroxapol.
- a biodegradable polymer, e g polyactic acid, polyglycolic acid, and copolymers of these.

Suitable intended combinations of the enhancing agents are, but are not limited to:

- 20 Lipids (also those disclosed in PCT application no. SE 98/01790) and surfactants, eg monoolein and sodium taurocholate, monoolein and Tween 80;

Lipids of non-phospholipids character (also those disclosed in SE 98/01790) and phospholipids, e g medium chain glycerides and lecithins;

- 25 Lipids (also those disclosed in SE 98/01790) and block copolymers, e g monoolein and Pluronic F 127;

Surfactants and oils, e g sucrose fatty acid esters and soy bean oil; and

Polymers and lipids, e g polycarbophil and monoolein.

The combinations might be in the form of emulsions and microemulsions comprising e g monoolein/triglyceride/water or isopropyl myristate/lecithin/water.

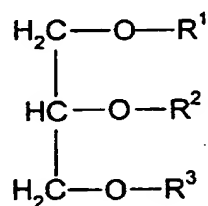
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Preferred additives of the invention are

- nonionic surfactants, such as sugar glycosides and sugar fatty acid esters;
- lipids, such as a phospholipid e g DPPC and DMPC;
- an oil, such as soy bean oil and sunflower oil;
- 10 - a chelating agent, e g EDTA, EGTA, citric acid;
- a fatty acid derivative of carnitine or a peptide; e.g. palmitoyl-DL-carnitine;
- polymer, such as polyacrylic acid, e g Carbopol, polycarbophil
- a block copolymer, e g a poloxamer, poloxamine and meroxapol;
- a saponin;
- 15 - the combinations listed above.

Lipids referred to above as disclosed in PCT application no. SE 98/01790 are a medium chain glyceride or a mixture of medium chain glycerides, particularly those having the formula

20



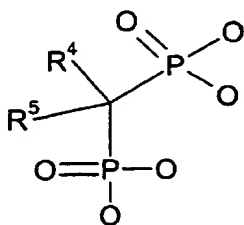
wherein R^1 , R^2 and R^3 are the same or different and each represent a hydrogen atom or an alkanoyl chain having 6 to 18 carbon atoms, preferably 6 to 12 carbon atoms, provided that at least one of R^1 , R^2 and R^3 is an alkanoyl group.

25

The dosage form used may be a solid, semisolid or liquid preparation prepared by techniques which are known *per se*. Usually the active substance will constitute between 0.001% and 99% by weight of the preparation, preferably 0.003 to 1.3 % by weight, most preferably 0.1 to 1%.

5

Preferably, the bisphosphonate has the general formula II



10 wherein

R^4 is H, OH or Cl; and

R^5 is

- 15 (a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;
- (b) halogen;
- (c) arylthio, preferably chlorosubstituted;
- (d) cycloalkylamino with 5 to 7 carbons; or
- 20 (e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

Alkyl groups in alkylamino and dialkylamino may have 1 to 5 carbon atoms and may be combined independently in the dialkylamino group.

25

The term "heterocyclyl" means a saturated or unsaturated 5 to 7- membered heterocyclic group with one or two rings and 1 to 3 heteroatoms, independently chosen from N, O and S.

- 5 Unless otherwise stated or indicated, the term "aryl" denotes a substituted or unsubstituted phenyl, furyl, thienyl or pyridyl group, or a fused ring system of any of these groups, such as naphthyl.

The term "substituted" denotes an aryl group as defined above which is substituted by one
10 or more alkyl, alkoxy, halogen, amino, thiol, nitro, hydroxy, acyl, aryl or cyano groups.

Compounds of the formula II include:

- 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate),
N,N-dimethyl-3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid
15 (mildronate,olpadronate),
1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid (ibandronate),
1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid (risedronate),
1-hydroxyethylidene-1,1-bisphosphonic acid (etidronate),
1-hydroxy-3-(1-pyrrolidiny)propylidene-1,1-bisphosphonic acid,
20 1-hydroxy-2-(1-imidazolyl)ethylidene-1,1-bisphosphonic acid (zoledronate),
1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene-1,1-bisphosphonic acid
(minodronate),
1-(4-chlorophenylthio)methylidene-1,1- bisphosphonic acid (tiludronate),
1-(cycloheptylamino)methylidene-1,1-bisphosphonic acid (cimadronate, incadronate),
25 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate)
and pharmaceutically acceptable salts thereof.

The most preferred compounds of the formula II are 4-amino-1-hydroxybutylidene-1,1-
bisphosphonic acid (alendronate) and its pharmaceutically acceptable salts.

In a preferred form, the pharmaceutical formulation according to the invention is adapted for oral administration and may be given during fasted or fed conditions.

In the preparation of pharmaceutical formulations according to the invention in the form of dosage units for oral administration, the bisphosphonate and the absorption enhancing agent may be filled into soft or hard gelatine or cellulose capsules; mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient; with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into particulate forms, granules or pressed into tablets.

In one embodiment of the invention the bisphosphonate and the additive is mixed into a suitable form considering that a particulate (solid, semisolid or liquid) form might be preferably chosen to avoid the presentation of the drug in high local concentrations that might be irritating at the mucosal membranes. Such particulate forms can be obtained by well known procedures, such as dispersing the bisphosphonate as a micronised powder ($< 10 \mu\text{m}$) in a suitable medium like sesam oil, soya oil etc, or by forming a carrier/drug system in particulate form. Micronised bisphosphonates or carrier/drug systems can be prepared by techniques such as but not limited to dry or wet milling, freeze milling, air-jet micronisation, spray drying, spray chilling, spray freeze drying, electrospraying, supercritical crystallisation (RESS or GAS methods), emulsion solvent evaporation, emulsion solvent extraction and emulsion solvent diffusion.

This suspension of the bisphosphonate in oil or the carrier/bisphosphonate system is then administered orally as a suspension or in capsules.

Suitable daily doses of bisphosphonates in therapeutic treatment of humans are about 0.001 to 100 mg/kg body weight at peroral administration, preferably 0.001 to 10 mg/kg, most preferably 0.005 to 0.3 mg/kg.

The enhancing agent, or the combination of enhancing agents, and a suitable carrier or non-functional excipients when needed will constitute between 0.1 to 99.9% by weight of the preparation, preferably between 80% to 99.9% by weight.

5

The pharmaceutical formulations according to the invention are useful for inhibiting bone resorption and thus for the treatment or prevention of bone loss related to osteoporosis, age, steroid therapy, rheumatism, Paget's disease or cancer. The pharmaceutical formulation according to the invention are also useful in the prevention and/or treatment of secondary
10 osteoporosis except steroid induced osteoporosis, periodontitis, osteoarthritis. The pharmaceutical formulations according to the invention are further useful for the treatment of hypercalcaemia. Consequently, the use of the said pharmaceutical formulations for treating these conditions are additional aspects of the invention.

- 15 In another aspect the invention provides a process for the preparation of a pharmaceutical formulation according to the invention, said process comprising forming a mixture of (i) bisphosphonate, (ii) an additive, and (iii) a pharmaceutically acceptable carrier.

In a further aspect the invention provides the use of bisphosphonate in conjunction with an
20 absorption enhancing agent for the manufacture of a medicament for the inhibition of bone resorption, or thus for the treatment or prevention of bone loss related to osteoporosis, age, steroid therapy, rheumatism, Paget's disease or cancer. The pharmaceutical formulation according to the invention are also useful in the prevention and/or treatment of secondary osteoporosis except steroid induced osteoporosis, periodontitis, osteoarthritis. Preferably,
25 the said medicament is adapted for oral administration.

In yet a further aspect the invention provides a method for the inhibition of bone resorption, or thus for the treatment or prevention of bone loss related to osteoporosis, age, steroid therapy, rheumatism, Paget's disease or cancer. The pharmaceutical formulation
30 according to the invention are also useful in the prevention and/or treatment of secondary osteoporosis except steroid induced osteoporosis, periodontitis, osteoarthritis, which

method comprises administering to a mammal, including man, in need of such treatment an effective amount of a pharmaceutical formulation according to the invention. Preferably, the said pharmaceutical formulation is administered orally.

5 **Biological evaluation**

The effectiveness of formulations according to the present invention to prevent bone loss has been analyzed in studies using intact young growing rat model, developed and well established to predict the effectiveness of bisphosphonates in later clinical practise.

10

Results

ED₅₀ values obtained in the intact rat model show that orally administered formulations according to the invention that have been tested are more potent than equimolar bisphosphonate alone.

15 In a 14-day study of intact young growing rats a clear dose-response effect of enhancer was found. No effects were found for bisphosphonate in saline and given per os.

The effects on bone density obtained with enhancer/bisphosphonate was similar to what was obtained with bisphosphonate given subcutaneously, while no effect was found for bisphosphonate in saline given per os.

20 All rats appeared normal and gained normal weight.

Conclusions

The rat studies strongly support the concept that enhancers as suggested in the present specification can increase the oral bioavailability of a bisphosphonate as disclosed in the present specification even in the presence of food.

25

Examples

Examples of pharmaceutical formulations according to the invention:

5 *Formulation 1*

Alendronate	2.3 mg
Caprylic acid, sodium salt	11.5 mg
50 mM Tris with 100 mM NaCl (buffer)	1.0 g

10 Approx. 2.3 mg alendronate and 11.5 mg caprylic acid was dissolved in buffer and pH adjusted to 7.5 using sodium hydroxide.

Formulation 2

Alendronate	2.3 mg
15 Monoolein	11.5 mg
Tween 80	11.5 mg
50 mM Tris with 100 mM NaCl (buffer)	1.0 g

20 Approx. 2.3 mg alendronate and 11.5 mg monoolein was dissolved in buffer containing Tween 80 and pH adjusted to 7.5 using sodium hydroxide.

Formulation 3

Alendronate	2.3 mg
Quil A	11.5 mg
25 50 mM Tris with 100 mM NaCl (buffer)	1.0 g

Approx. 2.3 mg alendronate and 50 mg Quil A was dissolved in buffer and pH adjusted to 7.5 using sodium hydroxide.

Formulation 4

Alendronate	2.3 mg
Carbopol 934P	5.0 mg
50 mM Tris with 100 mM NaCl (buffer)	1.0 g

5

Approx. 2.3 mg alendronate and 5.0 mg Carbopol was mixed with buffer to form a dispersion and pH adjusted to 7.5 using sodium hydroxide.

Formulation 5

10 Alendronate	2.3 mg
Carbopol 934P	15.0 mg
50 mM Tris with 100 mM NaCl (buffer)	1.0 g

15 Approx. 2.3 mg alendronate and 15.0 mg Carbopol was mixed with buffer to form a dispersion and pH adjusted to 7.5 using sodium hydroxide.

Formulation 6

Alendronate	2.3 mg
Isopropylmyristate	630 mg
20 Lecithin (Epicuron 200)	270 mg
50 mM Tris with 100 mM NaCl (buffer)	100 mg

25 Approx. 23 mg alendronate was dissolved in buffer and pH adjusted to pH 7.5 using sodium hydroxide and added to a mixture of isopropylmyristate and lecithin (70/30 w/w) while vortexing.

Formulation 7

Alendronate	2.3 mg
Isopropylmyristate	450 mg
30 Tween 21	450 mg

50 mM Tris with 100 mM NaCl (buffer) 100 mg

Approx. 23 mg alendronate was dissolved in buffer and pH adjusted to pH 7.5 using sodium hydroxide and added to a mixture of isopropylmyristate and Tween 21 (50/50 w/w) while vortexing.

Formulation 8

Alendronate 2.3 mg

Monoolein 630 mg

10 Soybean triglycerides 270 mg

50 mM Tris with 100 mM NaCl (buffer) 100 mg

Approx. 23 mg alendronate was dissolved in buffer and pH adjusted to pH 7.5 using sodium hydroxide and added to a mixture of monoolein and soybean triglycerides (70/30 w/w) while vortexing.

Formulation 9

Alendronate 2.3 mg

Soybean triglycerides 1.0 g

20 2.3 mg alendronate was added to soybean triglycerides and micronized using ultrasonication while cooling on ice.

CLAIMS

1. A pharmaceutical formulation comprising at least one bisphosphonate and one or more
of an additive agent, said additive being a substance selected from the group consisting
5 of

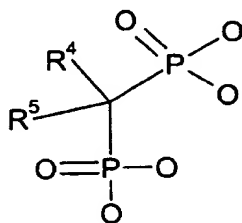
- a surfactant;
- an ampholytic surfactant;
- an anionic surfactant;
- a cationic surfactant;
- 10 - a bile salt;
- a soap and a fatty acid, and a salt thereof;
- a lipid (with the exception of those disclosed in PCT application no. SE98/01790);
- an oil;
- an enamine;
- 15 - a chelating agent;
- a phenothiazine;
- a fatty acid derivative of carnitine or a peptide;
- a substance selected from the group consisting of azone, concanavalin A, a phosphate and
a phosphonate derivative, such as DL - α -glycerophosphate and 3-amino-1-
20 hydroxypropylidene-1,1-diphosphonate, diethyl maleate and diethylethoxymethylene
malonate;
- a product from Maillard reactions;
- a polymer;
- a chitosan and a chitosan derivative;
- 25 - a block copolymer; and
- a biodegradable polymer.

2. A pharmaceutical formulation according to claim 1, wherein the additive is a nonionic
surfactant.

3. A pharmaceutical formulation according to claim 2, wherein the nonionic surfactant is a sugar glycoside or a sugar fatty acid ester.
4. A pharmaceutical formulation according to claim 1, wherein the additive is a lipid.
5. A pharmaceutical formulation according to claim 4, wherein the lipid is a phospholipid.
6. A pharmaceutical formulation according to claim 1, wherein the additive is an oil.
7. A pharmaceutical formulation according to claim 6, wherein the oil is soy bean oil or sunflower oil.
8. A pharmaceutical formulation according to claim 1, wherein the additive is a chelating agent.
9. A pharmaceutical formulation according to claim 8, wherein the chelating agent is EDTA, EGTA or citric acid.
10. A pharmaceutical formulation according to claim 1, wherein the additive is a fatty acid derivative of carnitine or a peptide.
11. A pharmaceutical formulation according to claim 10, wherein the additive of the fatty acid derivative of carnitine or a peptide is palmitoyl-DL-carnitine.
12. A pharmaceutical formulation according to claim 1, wherein the additive is a polymer.
13. A pharmaceutical formulation according to claim 12, wherein the polymer is a polyacrylic acid.

14. A pharmaceutical formulation according to claim 1, wherein the additive is a block copolymer.
15. A pharmaceutical formulation according to claim 14, wherein the block copolymer is a poloxamer, a poloxamine or meroxapol.
16. A pharmaceutical formulation according to claim 1, wherein the additive is a saponin.
17. A pharmaceutical formulation according to claim 1, wherein the additive is a biodegradable polymer.
18. A pharmaceutical formulation according to claim 17, wherein the biodegradable polymer is polylactid acid or polyglucolic acid.
19. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid and a surfactant.
20. A pharmaceutical formulation according to claim 19, wherein the combination of the lipid and the surfactant is monoolein and sodium taurocholate, or monoolein and Tween 80.
21. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid of non-phospholipid character and a phospholipid.
22. A pharmaceutical formulation according to claim 21, wherein the combination of the lipid of non-phospholipid character and the phospholipid is a medium chain glyceride and a lecithin.
23. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid and a block copolymer.

24. A pharmaceutical formulation according to claim 23, wherein the combination of the lipid and the block copolymer is monoolein and Pluronic F 127.
- 5 25. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a surfactant and an oil.
26. A pharmaceutical formulation according to claim 25, wherein the combination of the surfactant and the oil is a sucrose fatty acid ester and soy bean oil.
- 10 27. A pharmaceutical formulation according to claim 1, wherein the additive is a combination of a polymer and a lipid.
28. A pharmaceutical formulation according to claim 27, wherein the combination of the polymer and the lipid is polycarbophil and monoolein.
- 15 29. A pharmaceutical formulation according to claim 1, wherein the combination of additives is chosen to form an emulsion or a microemulsion.
- 20 30. A pharmaceutical formulation according to any one of claims 1 to 29 wherein the said bisphosphonate has the formula II



II

25 wherein

R⁴ is H, OH or Cl, and

R⁵ is

- (a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;
- (b) halogen;
- (c) arylthio or chlorosubstituted arylthio;
- (d) cycloalkylamino with 5 to 7 carbons; or
- (e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

31. A pharmaceutical formulation according to claim 30 wherein the bisphosphonate has the formula II

wherein

R⁴ is H or OH and

R⁵ is

- (a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;
- (d) cycloalkylamino with 5 to 7 carbons; or
- (e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

32. A pharmaceutical formulation according to claim 30 wherein the bisphosphonate has the formula II

wherein

R⁴ is OH and

R⁵ is

- (a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;
- (d) cycloalkylamino with 5 to 7 carbons; or

(e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

33. A pharmaceutical formulation according to claim 30 wherein the bisphosphonate is
- 5 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate),
N,N-dimethyl-3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid
(mildronate,olpadronate),
1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid
(ibandronate),
- 10 1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid (risedronate),
1-hydroxyethylidene-1,1-bisphosphonic acid (etidronate),
1-hydroxy-3-(1-pyrrolidinyl)propylidene-1,1-bisphosphonic acid,
1-hydroxy-2-(1-imidazolyl)ethylidene-1,1-bisphosphonic acid (zoledronate),
1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene-1,1-bisphosphonic acid
- 15 (minodronate),
1-(4-chlorophenylthio)methylidene-1,1-bisphosphonic acid (tiludronate),
1-(cycloheptylamino)methylidene-1,1-bisphosphonic acid (cimadronate, incadronate),
6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate)
and pharmaceutically acceptable salts there of.

- 20 34. A pharmaceutical formulation according to claim 33 wherein the bisphosphonate is
alendronate (4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid) or
pharmaceutically acceptable salts there of.
- 25 35. A pharmaceutical formulation according to any one of claims 1 to 34 which is adapted
for oral administration.
- 30 36. A pharmaceutical formulation according to any one of claims 1 to 35 for inhibiting
bone resorption.

37. A pharmaceutical formulation according to any one of claims 1 to 35 for the treatment and prevention of osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis.

38. A pharmaceutical formulation according to any of the preceeding claims wherein the formulation is in particulate form.

39. A pharmaceutical formulation according to claim 38 wherein the particulate form is solid, semisolid or liquid.

40. A pharmaceutical formulation according to any of claims 38 and 39 wherein the bisphosphone is in the form of micronized powder.

41. A process for the preparation of a pharmaceutical formulation according to any one of claims 1 to 40, comprising forming a mixture of (i) at least one bisphosphonate, (ii) an additive and (iii) a pharmaceutically acceptable carrier.

42. The use of a pharmaceutical formulation according to any one of claims 1 to 40 for the manufacture of a medicament for the inhibition of bone resorption.

43. The use of a pharmaceutical formulation according to any one of claims 1 to 40 for the manufacture of a medicament for the treatment and prevention of osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, or cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis.

44. A method for inhibition of bone resorption which comprises administering to a mammal, including man, in need of such treatment an effective amount of a pharmaceutical formulation according to any one of claims 1 to 40.

45. A method for the treatment and prevention of osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis, which comprises administering to a mammal, including man, in need of such treatment an effective amount of a pharmaceutical formulation according to any one of claims 1 to 40.

ABSTRACT

The present invention provides pharmaceutical formulations comprising at least one
5 bisphosphonate and an additive consisting of one or more absorption enhancing agents.
The said pharmaceutical formulations are useful for the inhibition of bone resorption and
for the treatment and prevention of osteoporosis.